REMARKS

Status of the Claims

Claims 2, 4, 6, 9, 14-19, 21-24, and 27 are currently pending. Claims 2, 4, 6, 9, 14-19, and 21-24 currently stand rejected. Claims 2, 4, 6, 9, 16, 17, 18, 19, 21, 22, and 24 are currently amended. New claim 27 has been added. Reconsideration and allowance of all of the pending claims is respectfully requested.

No new matter is being introduced into the Application by way of this amendment. Support for the amendments to claims 16 and 24, and for new claim 27, may be found at page 8, line 9 of the specification. The remaining amendments to the claims are editorial and merely correct claim dependencies.

Accordingly, entry of this amendment is appropriate and respectfully requested.

Claim Rejections - 35 U.S.C. § 103(a)

The Examiner rejects claims 2, 4, 6, 16, 17, 18, 22, 23 and 24 under 35 U.S.C. § 103(a) as unpatentable over Gorski et al. (*Clinical Chemistry*, 43(1):193-195, 1997) in view of Maatman et al. (*Biochem. J.* 288:285-290, 1992) and Simon et al. (*J. Biol. Chem.* 272(16):10652-10663, 1997).

The Examiner rejects claim 9 under 35 U.S.C. § 103(a) as unpatentable over Gorski et al. in view of Maatman et al. and Simon et al., and further in view of Kimura et al. (*J. Biol. Chem.*, 266(9):5963-5972, 1991).

The Examiner has also rejected claims 19 and 21 under 35 U.S.C. § 103(a) as unpatentable over Gorski et al. in view of Maatman et al. and Simon et al., and further in view of Galaske et al. (*Pflugers Archives Euro. J. Physiol.*, 375(3):269-277, 1978).

The Examiner rejects claims 14 and 15 under 35 U.S.C. § 103(a) as unpatentable over Gorski et al. in view of Maatman et al. and Simon et al., and further in view of Zuk et al. (United States Patent No. 4,281,061).

In view of the following remarks, as well as the Declaration pursuant to 37 C.F.R. §1.132 attached hereto, Applicants respectfully traverse the above rejections and request that the Examiner withdraw all rejections and allow the currently pending claims.

1. Gorski in view of Maatman and Simon

The Applicants respectfully assert that the prior art does not disclose or suggest the claim element of diagnosing or prognosing kidney disease. In addition, the Applicants respectfully assert that L-FABP and H-FABP are not equivalent as the Examiner suggests, and the combination of the Gorski and Matmaan references is improper. Therefore, the Applicants respectfully submit that Examiner has not borne the burden of factually establishing a *prima facie* case of obviousness of the present claims.

a.) Diagnosing kidney disease

"The Examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness." MPEP §2142. Thus, in order to make out a proper case of *prima*

facie obviousness, the Examiner must first factually demonstrate that the prior art meets the "diagnosing or prognosing" limitation of claim 16.

Gorski mentions the detection of FABP as follows: "The present data are the first to show that plasma FABP concentration is markedly increased in patients with chronic renal failure and normal heart function, similar to that found for myoglobin." Gorski, page 194, right column, 2nd para., lines 1-6. Gorski then mentions that: "[T]hese findings suggest that the kidney plays a more dominant role in the clearance of plasma FABP than of myoglobin." Gorski page 194, right column, 2nd para, lines 21-24.

However, the object of Gorski is to utilize FABP as a marker for diagnosing myocardial infarction. The FABP of Gorski is a heart type FABP (H- FABP) derived from the heart. Gorski does not even mention L-FABP, or the detection thereof. Gorski clearly did not contemplate the diagnosis of kidney disease by using H-FABP as a marker therefor. Moreover, in Gorski the specimen to be measured is plasma, and there is no teaching or suggestion of testing kidney tissue or urine.

As can be clearly seen from the section of Gorski cited above, Gorski only shows that FABP concentration increases in patients with chronic renal failure. See also Office Action. Page 12, first full paragraph. However as Gorski also states: "low molecular mass proteins such as FABP and myoglobin are cleared mostly by the kidney." Gorski, page 194, first column. Accordingly, Gorski merely demonstrates what was already known to those of skill in the art. In a patient with kidney failure, the FABP concentration will build up since it is no longer being cleared from the blood. Gorski does not disclose diagnosing or prognosing kidney disease as presently claimed.

The Examiner has therefore failed to make out a proper case of *prima facie* obviousness. In order to make out a proper case of obviousness in this case, the Examiner must factually show how Gorski meets the "diagnosing or prognosing" limitation of claim 16. Merely showing that FABP concentrations increase in the blood when a patients kidneys fail, does not disclose diagnosing or prognosing kidney disease. The Examiner has accordingly failed to bear the burden of making out a proper *prima facie* case of obviousness.

In Gorski throughout the entire disclosure, from the introduction (the object of research) to the final conclusion, FABP (H-FABP) is treated as a marker for the diagnosis of myocardial infarction. Gorski was attempting to show that the diagnosis of myocardial infarction in patients with chronic renal failure may be affected by erroneous interpretation of data. They obtained data for patients with normal heart function and chronic renal failure as the preinfarction data. In the conclusion Gorski discusses renal failure merely in relation with the diagnosis of myocardial infarction. (See Gorski, page 194, left column, lines 4-8; page 194, left column, lines 18-30; page 195, left column, lines 12-21; and page 195, left column, lines 25-36.

Accordingly, one skilled in the art would understand that the disclosure of Gorski is completely focused on the diagnosis of myocardial infarction. In order to obtain the present invention, it is necessary to add the diagnosis of kidney disease which is completely lacking from the cited references. This would result in completely changing the object of Gorski. The disclosure of Gorski would not lead one skilled in the art to the present invention.

Maatman includes a speculation with respect to the function of L-FABP, that L-FABP may bind to drugs and thereby may inhibit nephrotoxicity. But the possibility of inhibition of

nephrotoxicity with L-FABP does not suggest the possibility of diagnosis of kidney disease, as explained above.

Simon is concerned with control of expression of L-FABP. Simon discloses that a DNA sequence ("heptad repeat") existing in the upstream region of the L-FABP gene has a function of inhibiting expression of L-FABP. However, Simon does not teach or suggest the similarity or equivalency of L-FABP and H-FABP, and further does not teach or suggest the diagnosis of a kidney disease in human. The Examiner mentions that "Simon et al. was merely cited to further support a function of L-FABP in the kidney." See Office Action, page 14

Accordingly, the prior art does not disclose or suggest the invention as presently claimed. Withdrawal of this rejection is respectfully requested.

b.) L-FABP and H-FABP equivalence.

Gorski does not mention liver-type fatty acid binding protein. The Examiner uses Maatman to assert that the presently claimed liver-type fatty acid binding protein is equivalent to heart-type fatty acid binding protein. However, as the Examiner mentions in the Office Action, H-FABP and L-FABP are only 20-35% homologous. See Office Action, page 9, third line from bottom.

Since H-FABP and L-FABP clearly are not the same, in the present context "equivalent" can only mean equivalent with regard to the concentration building up in the blood as a result of renal failure. However, the Examiner has provided no evidence that H-FABP and L-FABP are even equivalent in this regard. The Examiner has completely failed to demonstrate that H-FABP and L-FABP are equivalent in the context of the present invention. The Examiner has thus again

failed to make out a proper *prima facie* case of obviousness with regard to the liver-type fatty acid binding protein element of claim 16.

As the Applicants demonstrate below, H-FABP and L-FABP are not at all similar or equivalent to each other. Maatman includes speculation with respect to the function of L-FABP and states that L-FABP may bind to drugs and thereby may inhibit nephrotoxicity. However, nephrotoxicity is a side effect induced by drugs, and it is not "kidney disease" as the Examiner seems to assert. That is, the possibility of inhibition of nephrotoxicity with L-FABP mentioned in the cited Maatman reference does not suggest the possibility of diagnosing kidney disease as presently claimed.

Maatman mentions that L-FABP and H-FABP exist in the kidney, but Maatman also mentions differences between L-FABP and H-FABP. The Examiner points out that Maatman discloses that L-FABP and H-FABP do not differ markedly with respect to the content at mRNA level by reference to the following statement of Maatman: "[B]ased on the RT-PCR and hybridization results, the content of the mRNAs of the liver and heart FABP types do not differ markedly in kidneys of male and female rats." See Maatman, page 289, left column, second paragraph, lines 8- 10 and Figure 6.

However, Maatman also discloses the results of detection at protein level (ELISA test), and that there were differences in the ratio of H-FABP and L-FABP: ELISA showed low amounts of liver type FABP in rat kidney cytosol (Table 2). The concentrations are much lower than those of the heart-type FABP, and the ratio of liver- and heart-type FABPs differs considerably from that in man." Maatman, page 288, left column, 2nd para. lines l-4, and Table 2.

Further, it is clearly mentioned in Maatman that H-FABP and L-FABP are different in ligand specificities with respect to the function of H-FABP and L-FABP: "[T]he significance of the occurrence in kidney of two FABP types with different ligand specificities requires further investigation." Maatman, page 289, right column, 2nd para, lines 10-12. Maatman also explains: "The liver-type FABP also binds some drugs [2,3], and may in this way prevent nephrotoxicity. The heart-type FABP only binds fatty acids and seems to be involved in lipid metabolism." Maatman, page 289, right column, 1st para, lines 8-10.

Moreover, it is mentioned in Maatman that there is a difference in cellular distributions. That is, H-FABP exists in the heart and the kidney but does not exist in the liver, but on the other hand L-FABP exists in the liver and kidney but does not exist in the heart. Further, and contrary to H-FABP, L-FABP exists topically in proximal tubules in humans. Maatman explains as follows:

> The rat heart FABP cDNA could be demonstrated on the blot . . . to be present in rat heart and kidney mRNA, but not in rat liver mRNA (Fig.6). The blot . . . showed the presence of liver FABP mRNA in both liver and kidney mRNA, but not in heart mRNA (Fig. 6).

Maatman, page 289, left column, 2nd para, lines 1-6, and Fig. 6. Maatman also explains:

> The cellular distribution of the heart-type FABP is similar in rat kidney to that previously found in human kidney [7]. The liver-type FABP however is restricted to the proximal convoluted and straight tubules in human kidney.

Maatman, page 288, right column, 1st para, lines 7-11.

Accordingly, as is made clear from the above, according even to Maatman it cannot be simply stated that H-FABP and L-FABP are similar/equivalent to each other. In fact, both are very different from a more comprehensive viewpoint.

As to the homology of H-FABP and L-FABP, even if there is about 25-35 % homology between H-FABP and L-FABP as the Examiner asserts, this still means that they are not homologous to 65-75 %.

Moreover, the H-FABP of Gorski is derived from the heart, but L-FABP is not found in the heart. This fact is mentioned not only in Maatman but also is supported by the following literature references that were filed with the response to a previous Office Action on July 22, 2003. See Exhibit 2, Van Nieuwenhovern at al,, Lipids, Vol. 31 Suppl: S223-S227, 1996, Table 2, and so on; and Exhibit 3, Veerkamp et at, Frog. Lipid Res., Vol. 34(1); 17-52, 1995, Table 3, and so on.

Thus, any person skilled in the art, particularly when referring to the combination of Gorski and secondary references such as Maatman, Simon and any others, will well understand that H-FABP and L-FABP are entirely different. With one being 'FABP existing in the heart' and another being 'FABP non-existing in the heart.'

As mentioned above, it is well understood in view of the cited references as well as other literature in the field, that H-FABP and L-FABP are very different. Therefore, it is submitted that the rejection is based upon an improper factual assumption. H-FABP and L-FABP are not similar and/or equivalent to each other, and cannot be substituted one for the other.

In order to make even more clear the differences between L-FABP and H-FABP, comparative experimental results are included herewith in the form of **Declaration by Takeshi SUGAYA** under 37 CFR §1.132.

As is clear from the comparative experimental results shown in Dr. Sugaya's Declaration under 37 CFR §1.132 attached hereto, L-FABP and H-FABP are not similar nor equivalent, and

the method of the present invention utilizing L-FABP shows superior results in comparison with a method utilizing H-FABP.

Accordingly, because the Examiner has failed to establish a proper case of *prima facie* obviousness, and because all of the elements of the present invention are not disclosed by the prior art, this rejection must now be withdrawn.

2. Gorski in view of Maatman, Simon, and Kimura

As discussed above, Gorski in view of Maatman and Simon completely fails to disclose or suggest the invention of the present claims. Gorski, Maatman, and Simon do not disclose or suggest diagnosing kidney disease with L-FABP. The addition of Kimura does not remedy the deficiencies of Gorski, Maatman and Simon. Accordingly, it is respectfully submitted that the rejection of claim 9 over Gorski in view of Maatman, Simon, and Kimura, must now be withdrawn.

3. Gorski in view of Maatman, Simon, and Galaske

As discussed above, Gorski in view of Maatman and Simon completely fails to disclose or suggest the invention of the present claims. Gorski, Maatman, and Simon do not disclose or suggest diagnosing kidney disease with L-FABP. The addition of Galaske does not remedy the deficiencies of Gorski, Maatman and Simon. Accordingly, it is respectfully submitted that the rejection of claims 19 and 21 over Gorski in view of Maatman, Simon, and Galaske, must now be withdrawn.

2. Gorski in view of Maatman, Simon, and Zuk

As discussed above, Gorski in view of Maatman and Simon completely fails to disclose or suggest the invention of the present claims. Gorski, Maatman, and Simon do not disclose or suggest diagnosing kidney disease with L-FABP. The addition of Zuk does not remedy the deficiencies of Gorski, Maatman and Simon. Accordingly, it is respectfully submitted that the rejection of claims 19 and 21 over Gorski in view of Maatman, Simon, and Zuk, must now be withdrawn.

Conclusion

It is respectfully submitted that in view of the above amendments and remarks, all of the pending claims are now in condition for allowance. An early reconsideration and Notice of Allowance is respectfully requested.

If the Examiner has any questions or comments, please contact Craig A. McRobbie (Registration No. 42,874) at the office of Birch, Stewart, Kolasch and Birch, LLP.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

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Respectfully submitted,

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